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March 12, 1999

Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 98D-1195

To the Documents Management Branch:

Thank you for this opportunity to comment on the Guidance for Industry on Bioanalytical Methods Validation for Human Studies.

We recognize that this Guidance is attempting to address the needs of a broad audience of bioanalytical scientists in a wide range of pharmaceutical companies, contract research organizations and academic institutions. We feel, however, that the Guidance would be more effective if several sections were further clarified.

In general, inclusion of a glossary providing clear definitions of terms would be a significant improvement. It should also be noted that, apart from a cursory statement on the first page, this document does not address the use of immunoassay, microbiological or other biologically based assays.

Specific comments, organized by section and page, are set out on the attached appendix.

Please do not hesitate to contact me if further clarification would be helpful.

Sincerely,

John W. A. Findlay, Ph.D.
Director, Bioanalytical
Pharmacokinetics, Bioanalytical and Radiochemistry

Enclosure

cc: Dr. P. Smith

98D-1195

C30

Appendix

Review of Draft Guidance for Industry on
Bioanalytical Methods Validation for Human Studies
Docket No. 98D-1195

Introduction

1. Bioanalysis in atypical matrices should not be required to adhere to the Guidance Document.

2. Why are GLP studies not included in the scope of the document?

Background

p2 "reproducibility" is not defined or used again. Define it. Is this the same as (2) "precision"?

Ref. Std.

p3 paragraph 1
We object to the idea of a "master std" - This cannot be achieved with commercially obtained standards or metabolites.

p3 line 2 change "samples" to "matrices".
paragraph 1, line 1 and 2 need clarification.

p3 paragraph A., Specificity: change to "6 male and 6 female individuals".

Pre-Study Validation

p3 last line and 1st line on p4 - aqueous solution not relevant - remove.

p4 paragraph 2 - eliminate, or refer to this being in "Method Development" rather than validation.

p4 paragraph 3, line 4 - remove "routinely".

p5 paragraph 1 " - comparison of mean" interference vs "mean" blank should be recommended rather individual comparisons.

p5 Linearity
line 1 - eliminate "with weighting".
line 7 - "4 out of 6" is inconsistent with "5 to 8 standards" (p4).
line 9 - remove "0.95 or greater correlation coefficient (r).

p5 Section C Precision, Accuracy Recovery
Make this a definition only paragraph.
There is general confusion in this paragraph which needs to be resolved by re-writing.

p6 paragraph 2, line 6 - remove criteria for recovery (50-60%)

D. Quality Control Samples
Change this heading to "Validation Samples". Quality control samples are run with study samples.

All of Section IV D
•object to use of 3 separate preparations each of standards and QCs.
•should not dictate number of batches.
•variance calculations should be done with ANOVA model because, as proposed, global statistics are underestimates of true between-run variation.

p7, IV E Please clarify "container system" - propose change to "container material".

p7, E 1. Freeze-Thaw
line 4- remove 'unassisted at room temperature" - needs to be same as sample treatment conditions.

Line 6 - add "for a minimum of" before "12 to 24 hours".

p8 line 1 & 2 - change to "thawed to room temp" - no consensus on the need for this experiment.

P8, E3 Long-Term Stability

line 9 - replace "standards" with "recovery controls"

p8 Formatting point: - last paragraph should be moved to left margin (of p7) since it refers to all of points 1-5.

p8-9 no criteria are specified for length of run.

p9 Specificity paragraph.

The criteria of 20% and 5% should refer to mean, not individual responses.

p6/9 for validation, low and LOQ QC should have 20% limit (not 15% for low). 15% limit is acceptable for QCs>3xLOQ. Otherwise LOQ will be forced to a higher concentration.

p9 Specificity, as stated here, is a "chromatography only" definition.

p9, V. In-Study Validation

p10 Paragraph 1, - last sentence: delete "All study samples from a subject should be analyzed in a single run".

p10 Paragraph 2, line 2

- define "nominal"
- If defined as weighed-in or theoretical, we disagree. Values should be set statistically by an appropriate number of assays.

P10 Paragraph 2
no discussion of dilution. QCs and their use relative to analysis of unknowns.

p10 Paragraph 3
delete "re-assays should be done in triplicate".

p11 Second set of bullets
#4 "reason for the missing samples" - delete if refers to study samples, clarify if refers to QC samples.

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